Docket No.: 066784-0013 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RESPONSE UNDER 37 CFR 1.116
EXPEDITED PROCEDURE

In re Application of	
Palsczewski et al.	Customer Number: 41552
Serial No.: 09/990,185	Confirmation Number: 1224
Filed: November 21, 2001	Group Art Unit: 1635
	Examiner: ANGELL, Jon E.

For: EXPRESSION OF POLYPEPTIDES IN ROD OUTER SEGMENT MEMBRANES

CERTIFICATE OF MAILING BY EXPRESS MAIL(37 CFR § 1.10) "Express Mail" Mailing Label Number EV 540 267 694 US

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR § 1.10 on the date indicated above and is addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on Aug 23, 2004.

Carrie Casey

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

I, Juan Ballesteros, declare as follows:

1) I am the Juan Ballesteros named as an inventor of the above-identified application.

2) I am co-founder and Vice President of Research at Novasite Pharmaceuticals. I have held this position since 1999. I received my Ph.D. in molecular biophysics from the Mount Sinai School of Medicine, New York, where I studied under a Fulbright scholarship. Prior to founding Novasite I completed postdoctoral research at both

Mount Sinai and Columbia University. A copy of my Curriculum Vitae is attached as Exhibit A.

3) I understand that the claims under examination stand rejected as allegedly lacking enablement, in part, because the Patent Office asserts that the claims lack a real world utility. Specifically, the Examiner alleges that there are less expensive alternative methods to produce the polypeptides of interest.

4) The claimed gene targeting construct that results in homologous recombination at a mouse rhodopsin gene and the claimed cell and mouse produced from the gene targeting construct are commercially useful for the production of large amounts of the transgenic polypeptide. The transgenic polypeptide can be purified and used in a variety of commercial settings.

5) The commercial usefulness of the claimed invention has been recognized by others. Specifically, Novasite is the recipient of two Small Business Innovation Research (SBIR) awards from the National Institutes of Health (NIH) for the purpose of producing transgenic mice that express a transgene of interest at the rhodopsin gene locus. A grant supporting expression and purification of serotonin receptors was awarded on July 31, 2003, and a copy of the award letter from the NIH is attached as Exhibit B. A contract for the production of endothelial differentiation gene (EDG) receptors was additionally awarded effective September 1, 2003, from the NIH. Novasite also has licensed the above-identified patent application to a well established public biotechnology company for the purpose of generating transgenic mice expressing large amounts of a transgene polypeptide as embodied in the claimed invention. At the request of our partner, the financial details of this multi-year collaborative agreement remain confidential.

6) In conclusion, I believe that the claimed invention has significant real world utility for producing transgenic mice that are useful as a bioreactor for generating large amounts of transgenic polypeptides. The recognition of this utility was shown by the filing of the above-identified application and has been corroborated by others through the award of an SBIR grant and an NIH contract and through the commercial licensing of the patent application.

Serial No.: 09/990,185

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date: 8/23/04

Signature: _____

Name: JUAN BALLESTEROS, PH.D.

Title: VICE PRESIDENT OF RESEARCH AND CSO

EXHIBIT A

NAME	POSITION TITLE
JUAN BALLESTEROS, Ph.D.	Vice President, Research

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEARS	FIELD OF STUDY
University of Barcelona, Spain	B.A.	1982- 87	Chemistry
Mount Sinai School of Medicine, CUNY	Ph.D.	1989 - 97	Biomedical Sciences

POSITIONS AND HONORS

Professional Experience

1997 Postdoctoral Fellow with Dr. Harel Weinstein, Mount Sinai School of Medicine, C.U.N.Y.

1999 Vice President, Research, Novasite Pharmaceuticals, San Diego, CA

Honors and Awards

1989-93 Fulbright scholar

SELECTED PEER-REVIEWED PUBLICATIONS (IN CHRONOLOGICAL ORDER)

1. Ballesteros, J.A. and H. Weinstein, *Analysis and refinement of criteria for predicting the structure and relative orientations of transmembranal helical domains.* Biophys J, 1992. **62**(1): p. 107-9.

2. Ballesteros, J.A. and H. Weinstein, *The role of Pro/Hyp-kinks in determining the transmembrane helix length and gating mechanism of a [Leu]zervamicin channel.* Biophys J, 1992. **62**(1): p. 110-1.

3. Pardo, L., J.A. Ballesteros, R. Osman, and H. Weinstein, *On the use of the transmembrane domain of bacteriorhodopsin as a template for modeling the three-dimensional structure of guanine nucleotide-binding regulatory protein-coupled receptors.* Proc Natl Acad Sci U S A, 1992. **89**(9): p. 4009-12.

4. Zhou, W., C. Flanagan, J.A. Ballesteros, K. Konvicka, J.S. Davidson, H. Weinstein, R.P. Millar, and S.C. Sealfon, *A reciprocal mutation supports helix 2 and helix 7 proximity in the gonadotropin-releasing hormone receptor.* Mol Pharmacol, 1994. **45**(2): p. 165-70.

5. Weinstein, H., D. Zhang, and J.A. Ballesteros, *Hallucinogens acting at 5-HT receptors: toward a mechanistic understanding at atomic resolution.* NIDA Res. Monogr., 1994. **146**: p. 241-62.

6. Sealfon, S.C., L. Chi, B.J. Ebersole, V. Rodic, D. Zhang, J.A. Ballesteros, and H. Weinstein, *Related contribution of specific helix 2 and 7 residues to conformational activation of the serotonin 5-HT2A receptor.* J Biol Chem, 1995. **270**(28): p. 16683-8.

7. Bramblett, R.D., A.M. Panu, J.A. Ballesteros, and P.H. Reggio, *Construction of a 3D model of the cannabinoid CB1 receptor: determination of helix ends and helix orientation.* Life Sci, 1995. **56**(23-24): p. 1971-82.

8. Ballesteros, J.A. and H. Weinstein, *Integrated methods for the construction of three dimensional models and computational probing of structure-function relations in G-protein coupled receptors*, , S.C. Sealfon, Editor. 1995. p. 366-428.

9. Fu, D., J.A. Ballesteros, H. Weinstein, J. Chen, and J.A. Javitch, *Residues in the seventh membrane-spanning segment of the dopamine D2 receptor accessible in the binding-site crevice.* Biochemistry, 1996. **35**(35): p. 11278-85.

10. Almaula, N., B.J. Ebersole, J.A. Ballesteros, H. Weinstein, and S.C. Sealfon, *Contribution of a helix 5 locus to selectivity of hallucinogenic and nonhallucinogenic ligands for the human 5-hydroxytryptamine2A and 5- hydroxytryptamine2C receptors: direct and indirect effects on ligand affinity mediated by the same locus.* Mol Pharmacol, 1996. **50**(1): p. 34-42.

11. Gether, U., S. Lin, P. Ghanouni, J.A. Ballesteros, H. Weinstein, and B.K. Kobilka, *Agonists induce conformational changes in transmembrane domains III and VI of the beta2 adrenoceptor.* Embo J, 1997. **16**(22): p. 6737-47.

12. Gether, U., J.A. Ballesteros, R. Seifert, E. Sanders-Bush, H. Weinstein, and B.K. Kobilka, *Structural instability of a constitutively active G protein-coupled receptor. Agonist-independent activation due to conformational flexibility.* J Biol Chem, 1997. **272**(5): p. 2587-90.

13. Konvicka, K., F. Guarnieri, J.A. Ballesteros, and H. Weinstein, *A proposed structure for transmembrane segment 7 of G protein-coupled receptors incorporating an asn-Pro/Asp-Pro motif.* Biophys J, 1998. **75**(2): p. 601-11.

14. Ballesteros, J., S. Kitanovic, F. Guarnieri, P. Davies, B.J. Fromme, K. Konvicka, L. Chi, R.P. Millar, J.S. Davidson, H. Weinstein, and S.C. Sealfon, *Functional microdomains in G-protein-coupled receptors. The conserved arginine-cage motif in the gonadotropin-releasing hormone receptor.* J Biol Chem, 1998. **273**(17): p. 10445-53.

15. Javitch, J.A., J.A. Ballesteros, H. Weinstein, and J. Chen, *A cluster of aromatic residues in the sixth membrane-spanning segment of the dopamine D2 receptor is accessible in the binding-site crevice.* Biochemistry, 1998. **37**(4): p. 998-1006.

16. Simpson, M.M., J.A. Ballesteros, V. Chiappa, J. Chen, M. Suehiro, D.S. Hartman, T. Godel, L.A. Snyder, T.P. Sakmar, and J.A. Javitch, *Dopamine D4/D2 Receptor Selectivity Is Determined by A Divergent Aromatic Microdomain Contained within the Second, Third, and Seventh Membrane-Spanning Segments.* Mol Pharmacol, 1999. **56**(6): p. 1116-1126.

17. Javitch, J.A., J.A. Ballesteros, J. Chen, V. Chiappa, and M.M. Simpson, *Electrostatic and aromatic microdomains within the binding-site crevice of the D2 receptor: contributions of the second membrane-spanning segment.* Biochemistry, 1999. **38**(25): p. 7961-8.

18. Liapakis, G, J.A. Ballesteros, S. Papachristou, W.C. Chan, X. Chen, and J.A. Javitch, *The forgotten Serine: A critical role for Ser203{super5.42} in ligand binding to and activation of the {beta}{sub2} adrenergic receptor.* J Biol Chem, 2000.

19. Norregaard L, Visiers I, Loland CJ, Ballesteros J, Weinstein H, and U. Gether, *Structural probing of a microdomain in the dopamine transporter by engineering of artificial Zn2+ binding sites.* Biochemistry, 2000. **39**(51): p. 15836-46.

20. Ballesteros, J.A., X. Deupi, M. Olivella, E.E. Haaksma, and L. Pardo, *Serine and threonine residues bend alpha-helices in the chi(1) = g(-) conformation.* Biophys J, 2000. **79**(5): p. 2754-60.

21. Javitch, J.A., L. Shi, M.M. Simpson, J. Chen, V. Chiappa, I. Visiers, H. Weinstein, and J.A. Ballesteros, *The fourth transmembrane segment of the dopamine D2 receptor: accessibility in the binding-site crevice and position in the transmembrane bundle.* Biochemistry, 2000. **39**(40): p. 12190-9.

22. Liapakis, G, J.A. Ballesteros, S. Papachristou, W.C. Chan, X. Chen, and J.A. Javitch, *The forgotten serine. A critical role for Ser-2035.42 in ligans binding to and activation of the beta 2-adrenergic receptor.* J Biol Chem, 2000. **275**(48): p. 37779-88.

23. Govaerts, C., C. Blanpain, X. Deupi, S. Ballet, J.A. Ballesteros, S.J. Wodak, G Vassart, L. Pardo, and M. Parmentier, *The TxP motif in the second transmembrane helix of CCR5: A structural determinant of chemokine-induced activation.* J Biol Chem, 2001. **276**(16): p. 13217-25.

24. Jensen, A.D., F. Guarnieri, S.G Rasmussen, F. Asmar, J.A. Ballesteros, and U. Gether, *Agonist-induced Conformational Changes at the Cytoplasmic Side of Transmembrane Segment 6 in the beta 2 Adrenergic Receptor Mapped by Site-selective Fluorescent Labeling.* J Biol Chem, 2001. **276**(12): p. 9279-9290.

25. Shi L, Simpson MM, Ballesteros JA, and J.A. Javitch, *The first transmembrane segment of the dopamine D2 receptor: accessibility in the binding-site crevice and position in the transmembrane bundle.* Biochemistry. 2001 **40**(41): p.12339-48.

26. Ballesteros, J. A., L. Shi, and J.A. Javitch, *Structural Mimicry in G-protein-coupled receptors: Implications of the high-resolution structure of rhodopsin for structure-function analysis of rhodopsin-like receptors.* Mol Pharmacol, 2001 **60**(1):1-19.

27. Ballesteros JA, Jensen AD, Liapakis G, Rasmussen SG, Shi L, Gether U, and J.A. Javitch, *Activation of the beta 2-adrenergic receptor involves disruption of an ionic lock between the cytoplasmic ends of transmembrane segments 3 and 6.* J Biol Chem. 2001 **276**(31): p. 29171-7.

28. Govaerts C, Lefort A, Costagliola S, Wodak SJ, Ballesteros JA, Van Sande J, Pardo L, and G Vassart, *A conserved Asn in transmembrane helix 7 is an on/off switch in the activation of the thyrotropin receptor.* J Biol Chem. 2001 **276**(25): p. 22991-9.

29. Visiers, I., H. Weinstein, and J. Ballesteros, *Methods for the Prediction and Molecular Modeling of Membrane Proteins: Application to G protein Coupled Receptors*. Methods in Enzymol. 2002: p. 343:329-71.

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********** NOTICE OF GRANT AWARD **********

SMALL BUSINESS INNOVATION RESEARCH PROG Issue Date: 07/31/2003

Department of Health and Human Services
National Institutes of Health
NATIONAL INSTITUTE OF MENTAL HEALTH

****

Grant Number: 1 R43 MH068919-01
Principal Investigator: SALOM, DAVID PHD
Project Title: Purified Serotonin Receptors for Structural Studies

VICE PRESIDENT, RESEARCH
NOVASITE PHARMACEUTICALS
11095 FLINTKOTE AVENUE
SAN DIEGO, CA 92121
UNITED STATES

Budget Period: 08/01/2003 - 01/31/2004
Project Period: 08/01/2003 - 01/31/2004

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $148,940(see ''Award Calculation'' in Section I) to NOVASITE PHARMACEUTICALS, INC. in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 42 CFR PART 52 15 USC 638 and is subject to terms and conditions referenced below.

Acceptance of this award including the Terms and Conditions is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Award recipients are responsible for reporting inventions derived or reduced to practice in the performance of work under this grant. Rights to inventions vest with the grantee organization provided certain requirements are met and there is acknowledgement of NIH support. In addition, recipients must ensure that patent and license activities are consistent with their responsibility to make unique research resources developed under this award available to the scientific community, in accordance with NIH policy. For additional information, please visit http://www.iedison.gov.

If you have any questions about this award, please contact the individual(s) referenced in the information below.

Sincerely yours,

Rebecca D. Claycamp
Grants Management Officer
NATIONAL INSTITUTE OF MENTAL HEALTH

See additional information below